REMARKS

Status of the Claims

Claims 1-8 and 11-21 were considered in the final Office action mailed on June 13, 2008. As reflected in the listing of claims beginning on page 2 of this paper, Applicants amend claims 2 and 3, add new claims 22-28 and cancel claims 1, 7, 8 and 16-19 herein. Support for the amendments and new claims can be found throughout the specification, claims and figures as originally filed, including, for example, at least at paragraph [0027] and at claims 3, 7 and 16-19 of the specification as originally filed. Applicants submit that no new matter is introduced by the amendments to the claims and new claims. Following entry of the amendments, claims 2-6, 11-15 and 20-28 will be pending for the Examiner's further consideration.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 3, 4, 12-14, 16, 17, and 21 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Office Action asserts that independent claim 3 results in the indication of a "predisposition to diabetes". Without acquiescing to the rejection and solely to advance prosecution, Applicants amend of independent claim 3 so that the preamble of the claim is now directed to a method for determining a predisposition to diabetes, which now matches the resolution of the claimed method. Applicants submit that support for the amendment can be found in the characterising portion of original claim 3. In view of the foregoing, Applicants urge reconsideration of the claims and withdrawal of the rejection of claims 3, 4, 12-14, 16, 17, and 21 under 35 USC 112, second paragraph.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 2-7 and 11-21 were rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Office Action asserts that no data is presented in the specification to support the underlying assumption of the claimed method that high concentrations of glycated insulin can be found in pre or early diabetics who still maintain normal glucose levels.

Applicants direct the Examiner's attention to Applicants' Figure 1, which separately show, for a control group and for three groups of type 2 diabetic patients, the group's mean glycated haemoglobin (HbA_{1c}), mean glucose and mean glycated insulin levels.

In the control group, the mean glucose levels were about 5mmol/l (within the normal range) and the mean HbA_{1c} levels were 5.7%.

The group of patients with good control had a mean duration of diabetes of 4.8 years (*see* Applicants' Table 1). This group of patients with good control had mean glucose levels of about 8mmol/l and their mean HbA_{1c} levels were 6.4%.

The group of patients with moderate control had a mean duration of diabetes of 7.1 years (*see* Applicants' Table 1). This group of patients with moderate control had mean glucose levels of about 13mmol/l and their mean HbA_{1c} levels were 7.9%.

The group of patients with poor control had a mean duration of diabetes of 8.5 years (*see* Applicants' Table 1). This group of patients with poor control had mean glucose levels of about 14mmol/l and their mean HbA_{1c} levels were 10.4%.

In summary, and looking solely at Applicants' Figures 1A and 1B, as the duration of diabetes increased, mean blood glucose levels and mean HbA_{1c} levels rose in parallel. What is surprising is that, in looking at Applicants' Figure 1C, glycated insulin levels were *highest* in those cohorts with the *shortest* duration of disease. This is surprising because a skilled man would have expected glycation of insulin to be directly correlated with mean glucose levels, as is the case for HbA_{1c}. In contrast, glycated insulin levels are *inversely* correlated with *mean glucose levels* and *duration of disease*.

Applicants submit that claims 2 and 3, as amended, enable one skilled in the art to make and/or use the claimed invention. Specifically, the skilled artisan is sufficiently enabled to early diagnose diabetes, or to determine prediabetes in an individual, by measuring whether the concentration of glycated insulin in a sample is at least about 20 pmol/l, without the need for undue experimentation.

In view of the foregoing, Applicants urge reconsideration of the claims and withdrawal of the rejection of claims 2-7 and 11-21 under 35 USC § 112, first paragraph.

Rejections under 35 USC 102(b): McKillop

Claims 2-7 and 11-21 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by McKillop *et al.* (August 2001, IDS) ("McKillop"). The Office action asserts that McKillop teaches the measuring of the concentration of glycated insulin in a biological sample in which the glucose levels are within the normal range, and whether or not the glycated insulin concentration is at least 20 pmol/ml. In this regard, the Office action specifically cites McKillop Figure 1, top right figure.

Applicants submit that McKillop's Figure 1 (top row of 3 individual figures) illustrates plasma glucose, plasma insulin, and plasma glycated insulin levels, respectively, in obese hyperglycaemic (ob/ob) mice ("Obese"), and lean littermate controls ("Lean"). More specifically, McKillop's Figure 1, top left panel, illustrates that mean glucose levels in lean mice are about 2.5 mmol/l, in contrast to mean glucose levels in obese mice that are about 21 mmol/l. McKillop's Figure 1, top middle panel, illustrates that mean insulin levels in lean mice are about 1 ng/ml, in contrast to mean insulin levels in obese mice that are about 21 ng/ml. McKillop's Figure 1, top right panel, illustrates that mean glycated insulin levels in lean mice are about 0.1 ng/ml, in contrast to mean glycated insulin levels in obese mice that are about 2.2 ng/ml.

With reference to the top right panel of McKillop's Figure 1, it is noted that the glycated insulin in obese mice is 2.2±0.1 ng/ml. Expressed as a molar concentration, 2.2 ng/ml glycated insulin, is 368.5 pmol/l. With reference made to the top left panel of McKillop's Figure 1, it is noted that the glucose in the same obese mice is about 21 mmol/l, which is well beyond the normal range.

The top row of 3 individual figures within Figure 1 of McKillop merely teaches that obese mice have higher levels of each of plasma glucose, plasma insulin, and plasma glycated insulin and that matched lean control mice have lower levels of each of plasma glucose, plasma insulin, and plasma glycated insulin. In particular, the top panel of McKillop's Figure 1 shows that increased plasma glucose levels correlate with each of increased plasma insulin levels and increased plasma glycated insulin levels. In contrast and, as is taught in the present Application at paragraph [0007] and in Figure 1, in diabetes, the concentration of glycated insulin decreases

over time with disease progression, and despite blood glucose concentration increasing over time with disease progression.

The claimed invention is novel over McKillop by disclosing that the predetermined concentration of glycated insulin of the invention should be at least 20 pmol/l, in a sample in which glucose levels are within a normal range. Moreover, as previously described herein, McKillop teaches that increased plasma glucose level correlates with each of increased plasma insulin level and increased plasma glycated insulin level, and so McKillop teaches away from determining a glycated insulin concentration of at least 20 pmol/l in a biological sample in which glucose levels are within a normal range.

The present invention is new and inventive over McKillop by demonstrating that the concentration of glycated insulin decreases over time with disease progression, and despite blood glucose concentration increasing over time with disease progression. The present Application demonstrates that glycated insulin levels are highest at the earliest stages of diabetes. More specifically, Table 1 of the present Application shows that the three type 2 diabetes patient cohorts are segregated by duration of diabetes, namely 4.8 ±0.6, 7.1 ±0.9, and 8.5±1.3 years. Referring now to Applicants' Figure 1, and the above submissions, it can be seen that plasma glucose levels increase with disease duration (Figure 1B), as do plasma glycated haemoglobin levels (Figure 1A). In contrast, plasma glycated insulin levels *decrease* with disease duration, indicating that glycated insulin levels are highest at the earliest stages of diabetes and, thereafter, that glycated insulin levels decrease with disease duration, and despite blood glucose concentration increasing over time with disease duration. Accordingly, Applicants submit that McKillop teaches away from Applicants' claimed invention.

Taken together, Applicants respectfully submit that the present invention is neither disclosed nor suggested by McKillop. In view of the foregoing, Applicants urge reconsideration of the claims and withdrawal of the rejection of claims under 35 USC § 102(b) over McKillop.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request allowance of claims 2-6, 11-15 and 20-28. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite allowance of this application, the Examiner is cordially invited to call the undersigned attorney.

Respectfully submitted,

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